

Smoking: A Risk Factor for Progression of Chronic Kidney Disease and for Cardiovascular Morbidity and Mortality in Renal Patients—Absence of Evidence or Evidence of Absence?

Stephan R. Orth* and Stein I. Hallan[†]

*Dialysis Center Bad Aibling, Bad Aibling, and Department of Internal Medicine II, University of Regensburg, Regensburg, Germany; and [†]Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, and Department of Medicine, Division of Nephrology, St. Olav University Hospital, Trondheim, Norway

Although it is beyond any doubt that smoking is the number one preventable cause of death in most countries, smoking as an independent progression factor in renal disease has been questioned against the background of evidence-based criteria. This is because information from large, randomized, prospective studies that investigate the effects of smoking on renal function in healthy individuals as well as in patients with primary or secondary renal disease are lacking. Since 2003, a substantial number of clinical and experimental data concerning the adverse renal effects of smoking have been published, including large, prospective, population-based, observational studies. These more recent data together with evidence from experimental studies clearly indicate that smoking is a relevant risk factor, conferring a substantial increase in risk for renal function deterioration. This review summarizes the present knowledge about the renal risks of smoking as well as the increased cardiovascular risk caused by smoking in patients with chronic kidney disease. The conclusion is that smoking is an important renal risk factor, and nephrologists have to invest more efforts to motivate patients to stop smoking.

Clin J Am Soc Nephrol 3: 226–236, 2008. doi: 10.2215/CJN.03740907

Chronic kidney disease (CKD) is a growing worldwide problem that is increasingly shown to be interwoven with cardiovascular disease (CVD) and smoking. The prevalence of CKD in Western populations is high (1–3), and the number of patients with ESRD has increased dramatically in the past few decades. This rise is expected to continue, particularly in developing countries, where smoking and other cardiovascular risk factors are increasing substantially (4,5), and will be paralleled by rising CKD- and ESRD-related costs (6,7).

A tight relationship between CKD and CVD has become apparent: On the one hand, CKD and its epiphenomena increase the risk for CVD (8); on the other hand, CVD accounts for the majority of morbidity and mortality in patients with CKD (6,9). Diabetes and hypertension are widely acknowledged risk factors for kidney damage, and data increasingly indicate that smoking can have a negative effect on the kidney (for review, see references [10–12]). The consequences of cigarette smoking for patients with CKD could be severe, affecting both the progression of CKD and CVD; however, this is not sufficiently acknowledged by physicians and patients with

CKD. The lack of any change in smoking behavior of patients who initiated renal replacement therapy between 2000 and 2005 (13) document the need to improve smoking cessation rates in renal patients.

This article reviews the current knowledge about (1) the adverse effects of smoking on kidney function, (2) the mechanisms of smoking-induced renal damage, and (3) the adverse effects of smoking on CVD morbidity and mortality in renal patients. In addition, we outline a feasible smoking cessation intervention adapted to renal patients.

Smoking-Associated Renal Risk

General Population

Until 2003, the data on the risk of smoking-associated CKD in patients of the general population were scarce. The Multiple Risk Factor Intervention Trial (MRFIT) investigated 332,544 men and documented that smoking was significantly associated with an increased risk for ESRD (14), but the magnitude of the effect was not reported, and no baseline creatinine and proteinuria measurements were available. The study by Pinto-Sietsma *et al.* (15) involved 7476 participants of the Prevention of Renal and Vascular Endstage Disease (PREVEND) trial. They found a correlation of urine albumin excretion rate with the number of cigarettes smoked. After adjustment for potential confounding factors, current smokers who smoked <20 or >20 cigarettes per day, respectively, had an elevated risk for high-

Published online ahead of print. Publication date available at www.cjasn.org.

Correspondence: Dr. Stephan R. Orth, Bahnhofstrasse 9, D-83043 Bad Aibling, Germany. Phone: 0049-170-2311948; Fax: 0049-08061-37925; E-mail: stephan.orth@gmx.net

normal urine albumin concentration (relative risk [RR] 1.33 and 1.98, respectively). Halimi *et al.* (16) studied 28,409 volunteers from the general population. They found that current and former smokers had a marked risk for macroalbuminuria (adjusted RR 3.26 and 2.69, respectively), indicating nonreversible kidney damage related to smoking. Smokers had a slightly but significantly higher creatinine clearance than nonsmokers, at least in men, leading to the hypothesis of smoking-induced hyperfiltration (11). The study of Briganti *et al.* (17), involving 11,247 randomly selected, population-based Australians, showed that lifetime smoking exposure was significantly associated with CKD stage 3 or more in men but not in women. This finding raised the hypothesis that men may be more susceptible to the adverse renal effects of smoking (18). Furthermore, lifetime smoking exposure was paralleled by an increment of urine protein excretion, independent of gender. This increase was particularly marked in individuals with high-normal systolic BP and postload glucose concentrations.

One of the first cohort studies that focused on change in kidney function related to smoking analyzed data that were obtained from 4142 nondiabetic participants of the Cardiovascular Health Study Cohort (19). After adjustment for potential confounding factors, the number of cigarettes smoked per day was highly correlated with progression of CKD. For every five cigarettes smoked per day, the RR for an increase in serum creatinine $\geq 27 \mu\text{mol/L}$ during a minimum of 3 yr increased by 31%. The corresponding increase per 10-mmHg rise in BP was 16%. Some other mostly small retrospective studies from this period documented a higher risk for increased urine albumin excretion indicating renal damage in smokers as compared with nonsmoker (for review, see references [10–12]).

Since 2003, smoking as a renal risk factor in the general population has been addressed in several studies. Two studies found no effect of smoking on renal function (20,21). The study by Vupputuri and Sandler (21) was a case-control study ($n = 1070$) that was penalized by its retrospective nature and investigation of incident CKD only. The other study used baseline data of the PREVEND trial (20). In a cross-sectional analysis, no contribution of smoking, cholesterol/HDL ratio, and antidiabetic medication was found; however, a large number of studies have documented a negative effect of smoking on renal function, the most important being that of Haroun *et al.* (22): The end point of this large, community-based, prospective cohort study of 20 yr duration was ESRD or kidney disease listed on the death certificate. Current cigarette smoking was associated with ESRD or CKD death in both men (hazard ratio [HR] 2.4) and women (HR 2.9). Similarly, current smoking had an adjusted HR of 1.84 for ESRD after 25 yr in a recent analysis of 12,866 randomly assigned men of the MRFIT (23).

A recent community-based 10-yr follow-up study from Japan investigating 123,764 individuals aged >40 yr (24) found that smoking was a predictor of CKD in men and women (RR for CKD stages 3 and 4 1.13 and 1.16, respectively). Equal risk in men and women was also found in a population-based, cross-sectional study from Norway involving 65,193 individuals (25). A significant, dosage-dependent increase in risk for CKD (GFR $<45 \text{ ml/min per } 1.73 \text{ m}^2$) in men and women was seen above

a cumulative lifetime cigarette exposure of 25 pack-years (adjusted RR 1.42 for 25 to 49 pack-years and 2.05 for >50 pack-years, respectively). Of note, the CKD risk was very high in individuals who, in addition to smoking >25 pack-years, were obese and physically inactive, pointing to the possibility of a biologic interaction of these lifestyle-related variables. In 2981 Italian individuals aged 65 to 84 yr, current smoking (>20 cigarettes per day) was the strongest independent predictor of a pathologic loss of renal function (odds ratio [OR] 2.3) (26). This was independent of baseline serum creatinine and argues for smoking being a very important risk factor for CKD in elderly individuals, also confirmed by a recent Southeast Asian population-based study (27).

Only a little information is available about the type of CKD associated with smoking. In a population-based, case-control study, Ejerblad *et al.* (28) documented that the strongest association was found with nephrosclerosis, but significant positive associations were also reported for glomerulonephritis. Taken together, recent studies clearly document that smoking, particularly heavy smoking and high cumulative smoking exposure, is an independent risk factor for CKD in both male and female individuals of the general population.

Patients with Diabetes

From 1978 to 2003, numerous studies (for review, see references [11,12]) accumulated evidence that smoking promotes the progression of all stages of diabetic nephropathy to a similar extent, both in type 1 and type 2 diabetes: It (1) increases the risk for development of microalbuminuria, (2) accelerates progression from the stage of microalbuminuria to macroalbuminuria, and (3) accelerates progression from early stages of diabetic nephropathy to ESRD. Some of these studies were hampered with methodologic problems, however.

Recent prospective studies have strengthened these earlier findings: De Boer *et al.* (29) reported important data from an observational extension of the randomized prospective Diabetes Control and Complications Trial (DCCT). Among 1105 patients with type 1 diabetes and normal urine albumin excretion at baseline, a 4.3-fold greater rate of GFR decline (measured by ^{125}I -iothalamate clearance) was observed in active *versus* non-active smokers (-0.77 *versus* $-0.18 \text{ ml/min per } 1.73 \text{ m}^2/\text{yr}$). Additional data were provided by a prospective observational study involving 227 white patients with type 2 diabetes and nephropathy (30). The patients were followed for 6.5 yr, and a mean of seven measurements of GFR (using $^{51}\text{Cr-EDTA}$ plasma clearance) was performed per patient over time. A faster rate of GFR decline was independently associated with heavy smoking. Several smaller prospective studies have confirmed the deteriorating effect of smoking (31–33).

A cross-sectional study that evaluated 32,208 patients with type 2 diabetes and without known albuminuria adds further information regarding the early stage of diabetic renal involvement (34). Smoking was an independent risk factor for increased urine albumin excretion. A follow-up study of 185 patients with type 1 and type 2 diabetes with and without nephropathy found that smoking independently was associ-

ated with a decrease of estimated GFR (35). This was also independent of proteinuria.

In summary, several recent studies document that smoking is a risk factor for all stages of diabetic renal damage. The impact on the rate of progression seems to be substantial, resulting in a shortening of the dialysis-free interval. Further studies to investigate the magnitude of the acceleration of progression rate and the dose-response relationship are necessary, however.

Patients with Primary Hypertension or Primary Renal Disease

It has long been known that smoking is a strong predictor of increased urine albumin in patients with primary hypertension (for review, see references [11,12]). A recently published prospective 7-yr study that investigated 225 patients (36) found that estimated GFR declined faster in patients with “severe” as compared with those with “mild” hypertension, and GFR declined faster in smokers *versus* nonsmokers, independent of urine albumin/creatinine ratio. Whether smoking also increases the risk for ESRD in these patients is unproved, however: A prospective study including 5730 black and 6182 non-black hypertensive men aged 52.5 ± 0.2 yr did not find an association between smoking and ESRD during a minimum of 13.9 yr of follow-up (37).

It seems plausible that the diseased kidney is particularly sensitive to the potential adverse effects of smoking. The available data on this issue are limited, however. A retrospective case-control study in patients with IgA glomerulonephritis and autosomal dominant polycystic kidney disease was the first to document an increased risk for ESRD in the 144 male patients investigated (38). The risk increased with the amount of cigarettes consumed over time. After adjustment for possible confounders, multivariate analysis revealed that the risk for ESRD was excessively high in patients who had not been treated with an angiotensin-converting enzyme inhibitor. A recent study of 554 patients with autosomal dominant polycystic kidney disease did not find, however, that cigarette smoking influences the disease course (39). Concerning systemic diseases with renal involvement, only two studies with contradictory results in patients with lupus nephritis are available (40,41).

Taken together, the evidence for smoking as a renal risk factor in patients with primary hypertension or primary renal disease is limited, and the available studies do not provide satisfactory proof for the adverse effect of smoking. More prospective studies are needed to get a definite answer.

Patients with a Renal Transplant

Important evidence documenting that smoking is a risk factor for progressive loss of renal graft function has accumulated during the past few years (for review, see references [11,42]). A cohort study of 645 adult renal allograft recipients found that smokers had significantly worse kidney graft survival as compared with nonsmokers (84, 65, and 48% at 1, 5, and 10 yr, respectively, *versus* 88, 78, and 62%). Pretransplantation smoking adversely affected death-censored graft survival in recipients of cadaveric ($P = 0.02$) and of living-donor kidneys ($P = 0.02$), independent of acute rejection episodes. In a multivariate

analysis, pretransplantation smoking was associated with a RR of 2.3 for graft loss. Among patients with a smoking history, death-censored graft survival was significantly improved by quitting smoking before transplantation. This finding is of major importance for the treatment of patients who have CKD and are considered for renal transplantation.

Other studies have also found a negative effect of smoking (43–45). Of the 279 patients who were investigated in an Austrian study (45), smokers had higher serum creatinine values (2.3 ± 2.7 *versus* 1.8 ± 1.4 mg/dl; $P = 0.21$) and tended to develop transplant failure (33.3 *versus* 21.2%; $P = 0.25$). Significance may have been missed as a result of insufficient statistical power, particularly because of the small number of smokers included in the study. Others found only a negative impact of smoking on graft survival, which was not censored for recipient death (46). Of note, one study documented that the donors' history of smoking was an independent risk factor for shortened graft survival (43). This deserves further investigation and, if confirmed, should be considered in the validation of organ quality.

New Insights into the Mechanisms of Smoking-Induced Renal Damage

Investigations of the mechanisms underlying the adverse renal effects of smoking are hampered by several factors. First, renal susceptibility genes or polymorphisms may play a role, influencing the magnitude of the nephrotoxic effect of smoking in different individuals. Second, it has become clear that multiple complex and heterogeneous mechanisms play a role. This may be complicated by several yet unidentified confounding factors that are associated with smoking or interact with smoking. Third, more than 4000 chemicals in the form of particles and gases that are found in cigarette smoke could be responsible for its nephrotoxic effect. Potential mediators of smoking-induced renal damage can be subdivided into nonhemodynamic and hemodynamic mechanisms. An overview of potential mechanisms is given in Figure 1.

Nonhemodynamic Mechanisms as Potential Mediators of Smoking-Induced Renal Damage

Endothelial cell dysfunction, activation of growth factors (angiotensin II, endothelin-1, and TGF- β_1), tubulotoxic effects, oxidative stress, increased clotting of platelets, impaired lipoprotein and glycosaminoglycan metabolism, modulation of immune mechanisms, vasopressin-mediated antidiuresis, and insulin resistance all are affected by smoking exposure (for review, see references [11,12,47]). We focus on more recent data that implicate additional mechanisms.

In an *in vitro* study that used human mesangial cells, Jaimes *et al.* (48) reported that nicotine induced cell proliferation and increased fibronectin production by 50%. Both mesangial cell proliferation and increased production of fibronectin are players in the progression of CKD. This study documented that nicotinic acetylcholine receptors, which mediate cell proliferation (49), are expressed on human mesangial cells. A study that used rat mesangial cells documented that exposition of these cells to cigarette smoke concentrate induced an increase of

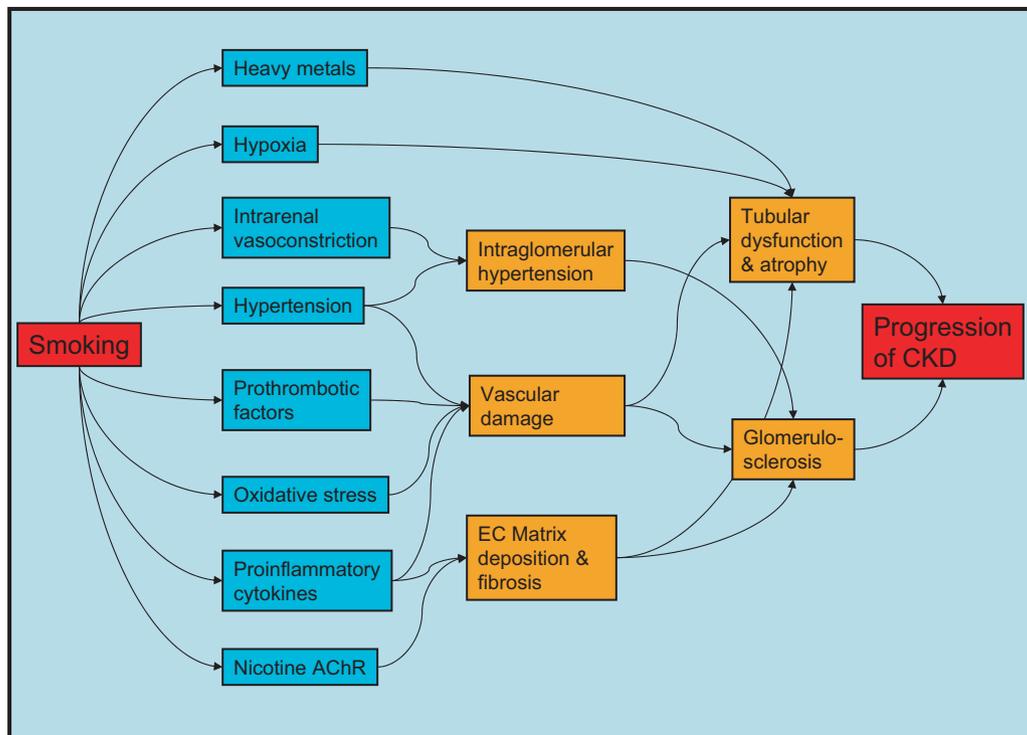


Figure 1. Overview of some potential mechanisms for smoking-induced renal damage. AChR, acetylcholine receptor; CKD, chronic kidney disease; EC, extracellular.

TGF- β_1 , a major player in the genesis of renal fibrosis, and 8-epi-PGF 2α , a marker of lipid peroxidation (50). Similar results were found in other experimental models and in humans (51–53). It is interesting that in nonmacroalbuminuric patients with type 2 diabetes, cessation of smoking led to a significant reduction of urine TGF- β_1 excretion, which implicates a beneficial effect of smoking cessation on progression of early diabetic renal damage.

Other environmental and occupational exposures may influence the magnitude of renal damage that is conferred by smoking. Cigarette smokers are exposed to significant amounts of cadmium (Cd) and lead (Pb) (54), which accumulate in kidney tissue more than in any other organ and are toxic at very low dosages (55). According to studies from Egypt, smoking has toxic effects on tubular cells, which are synergistic to occupational Pb (56), mercury (57), and silica (58) exposure. Dietary Cd and Pb seems to confer mild tubular dysfunction, whereas dietary exposure plus cigarette smoking is associated with tubular plus glomerular dysfunction (59). The dietary risk for renal Cd toxicity in the general population of the United States (60) and Japan (61) seems to be negligible, provided that no additional exposures from other sources are present. Concerning Cd, smoking 20 cigarettes per day for longer periods of time leads to 45 to 70% higher accumulation dosages of Cd in the renal cortex (60). In patients who are at high risk for CKD, the burden of cumulative exposure to these nephrotoxins that is conferred by smoking may increase its impact on the kidney: In individuals with diabetes, low-level Cd exposure has been associated with early onset of diabetic nephropathy (62). De-

spite the compelling evidence for a causal relationship between smoking and these mechanisms, the magnitude of the effect of the various mechanisms that contribute to renal damage remains unclear.

Hemodynamic Mechanisms as Potential Mediators of Smoking-Induced Renal Damage

BP and heart rate are increased by smoking, which for the major part is due to the action of nicotine (for review, see reference [10]). Because increased BP is one of the most important factors promoting progression of CKD, it is likely to play an important role in mediating smoking-induced renal damage. The rise in BP is due to an increase in cardiac output and total peripheral vascular resistance. The BP rise appears immediately and occurs before any increase in circulating catecholamines (for review, see reference [63]). Some data implicate an alteration of the diurnal rhythm of BP in smokers (e.g., a lower night/day ratio of systolic and diastolic BP in healthy smokers as compared with nonsmokers [64]). Because alterations of the day/night BP profile do have a notable impact on renal (65) and cardiovascular (66) risk, more data on this issue would be of importance. It is of note that smoking interacts with the effects of some antihypertensive drugs. At least in nonrenal patients, smoking blunts the antihypertensive effect of β blockers (67). Furthermore, in the short term, cigarette smoking blunts the beneficial effect of amlodipine on arterial stiffness (68).

Besides the aforementioned changes in systemic hemodynamics, smoking alters intrarenal hemodynamics. This has pre-

viously been reviewed in detail (10). In brief, the data available led to the hypothesis of increased glomerular pressure induced by smoking as a result of impaired renal autoregulation, at least in patients with renal disease. In healthy individuals, an increase in renal vascular resistance is observed. This is thought to be “physiologic” and to protect the glomeruli from the increase in systemic BP, resulting in unchanged intraglomerular pressure. The physiologic increase in renal vascular resistance is inhibited by pretreatment with a β blocker (69), which led to the hypothesis of smoking-induced β_1 receptor-mediated renin and angiotensin II production (12).

Histopathologic Features of Smoking-Induced Renal Damage Bangstad *et al.* (70) prospectively investigated 18 patients with type 1 diabetes and microalbuminuria over 8 yr, and a renal biopsy was performed at baseline and at the end of the study. The progression of glomerular structural damage (matrix and mesangial/glomerular volume fractions, basement membrane thickness) was more pronounced in smokers than in nonsmokers. Baggio *et al.* (71) performed a renal biopsy study in 96 patients with type 2 diabetes and found that heavy smoking was associated with increased glomerular basement membrane thickness.

Lhotta *et al.* (72) investigated 107 patients with CKD. Most of them had glomerular disease with marked proteinuria and uncontrolled BP. The only histopathologic alteration associated with smoking in male patients was more severe myointimal hyperplasia of intrarenal arterioles. Concerning histopathologic findings in patients with a renal transplant, the same group reported that fibrous intimal thickening of small arteries was the only significant lesion associated with smoking (45). Besides the aforementioned study, only one more study in patients with primary renal disease is available: Myllymaki *et al.* (73) investigated 202 patients with IgA glomerulonephritis. No correlation of smoking habits with histopathologic changes was observed.

Concerning smoking-induced structural alterations of the kidneys of individuals of the general population without apparent renal disease, only little information is available. Arteriolar wall thickening, mainly as a result of fibroelastic intimal proliferation and hyaline thickening in the intima, has been reported, however (for review, see references [10–12]). These findings support the notion that the major part of CKD found in smokers of the general population is related to nephrosclerosis (28). The susceptibility of individuals to develop renal vascular sclerosis is probably influenced by gene mutations (74), an issue that certainly will be of major interest in the future. That smoking is a risk factor for ischemic nephropathy, which is an increasing cause of ESRD in elderly individuals, is undisputed (for review, see reference [12]).

Idiopathic nodular glomerulosclerosis has been linked to heavy smoking (75). Fewer than 50 cases have been documented in the literature so far (76). Median time from biopsy to ESRD is only 26 mo in one series (77). In cases of rapid CKD progression in heavy smokers, even in those who quit several years before (77) or do not have other risk factors that might result in vascular injury (78), this disease should be considered.

Nasr and D’Agati (77) proposed to term this entity “smoking-associated nodular glomerulosclerosis,” because the term “idiopathic” does not stand against the evidence of the strong association of nodular glomerulosclerosis with smoking.

Taken together, the histopathologic changes that are conferred by smoking mainly affect the renal artery and the intrarenal arterioles. Potential effects on the glomerular and tubulointerstitial structure seem to be subtle, and larger biopsy studies are needed to investigate this issue further.

Smoking and Cardiovascular Disease and Mortality Risk in Renal Patients

Mortality is high in patients with CKD and outnumbers that observed in the general population by a factor of 10 to 20, with >50% of this excess burden being attributable to CVD (79). The association between smoking and cardiovascular mortality has been documented beyond any doubt in the general population (80). In contrast, the data available in patients with CKD are limited. Because the cardiovascular risk increases with the degree of renal function impairment (81), we discuss patients who have CKD and are in the predialysis phase and patients who have CKD with ESRD that requires dialysis separately. Finally, the specific situation of patients after renal transplantation is addressed.

Patients with CKD (Predialysis Phase)

In a prospective cohort study of 147 patients with stage 3 CKD, the cumulative smoking exposure has been reported to be highly significantly associated with fatal cardiovascular accidents (82). This was confirmed by recent data from the Cardiovascular Health Study that investigated 5808 patients who were ≥ 65 yr of age and had CKD (83). Traditional risk factors including smoking were associated with the largest absolute increases in risks for cardiovascular deaths among patients with CKD. For current smoking, there were 20 extra deaths per 1000 patient-years, which was topped only by left ventricular hypertrophy (25 extra deaths per 1000 patient-years). The association of several risk factors for coronary artery disease (CAD) was studied among participants with CKD in the population-based Atherosclerosis Risk in Communities Study (ARIC) (84). The RR for CAD was 1.65 for current smoking, 2.02 for hypertension, 3.06 for diabetes, and 1.96 for anemia. This study is important because it documents that CAD risk factors that are known from studies in the general population remain predictive among patients with CKD.

Peripheral arterial disease (PAD) as an important manifestation of atherosclerosis is highly prevalent in patients with CKD (85) and contributes substantially to the increased morbidity and mortality in patients with CKD (86). In individuals of the general population, current smoking has been shown to be the most important independent risk factor for PAD (87). In patients with IgA glomerulonephritis, smoking has been reported to be an independent risk factor for vascular disease (88). In patients with type 2 diabetes, smoking is independently associated with carotid intima media thickness (89), a predictor of cardiovascular disease and all-cause mortality (90).

Patients with ESRD

Smoking is an independent risk factor for arterial calcification in patients with ESRD, which is associated with increased cardiovascular risk (91). CAD and PAD are particularly common in dialysis patients. In a prospective, single-center study that investigated all incident hemodialysis patients from 1997 to 2003, Koch *et al.* (92) reported that, at the start of hemodialysis treatment, 38 and 14% of the patients had CAD and critical limb ischemia (CLI), respectively. Patients with CAD and CLI were more likely to be smokers. Smoking, CLI, and age independently increased the risk for death (HR 2.3, 4.9, and 1.1, respectively). Smoking, besides other traditional cardiovascular risk factors, has been documented to be an independent risk factor for CAD and PAD in patients with ESRD (93). A cross-sectional analysis of a random sample ($n = 4025$) of incident patients with ESRD from the Dialysis Morbidity and Mortality Study, Wave 2, revealed that smokers had a 22% greater likelihood of having CAD than nonsmokers (94). The adjusted OR was 1.44 for smokers *versus* never smokers. Other studies also found an association of smoking with CVD (95,96).

An important study that documented that smoking increases cardiovascular morbidity and mortality in hemodialysis patients is that of Foley *et al.* (97). They found that current smoking was independently associated with new-onset congestive heart failure (HR 1.59), new-onset PAD (HR 1.68), and mortality (HR 1.37). This was confirmed by a study that used the Cardiovascular Risk Extended Evaluation cohort database (98).

Patients with a Renal Transplant

The annual risk for a fatal or nonfatal CVD event is 3.5 to 5.0% in kidney transplant recipients (50-fold higher than in the general population [99]). It is undisputed that smoking is a risk factor that amplifies the risk for fatal and nonfatal CVD events in kidney transplant recipients (100–104). A recent cohort study (101) that investigated all patients who were ≥ 60 yr of age and received a cadaveric renal transplant between 1985 and 2000 in Quebec, Canada, reported that the only modifiable risk factors that were independently associated with patient survival were smoking at the time of transplantation (HR 2.09), body mass index (HR 1.34), and time on dialysis before transplantation (HR 1.1). The data document that smoking is by far the strongest modifiable predictor of mortality in these elderly patients. These data have largely been confirmed by others (104), even in younger individuals (102). The magnitude of the negative effect of pretransplantation smoking is quantitatively similar to that of diabetes (102). A case-control study documented that diabetes (OR 5.56), smoking (OR 3.56), and a previous transplant (OR 2.81) were independently associated with acute coronary syndrome within 2 yr after renal transplantation (105). Thirty-seven percent of early acute coronary syndrome occurred perioperatively, the majority in the first 3 mo after transplantation. This finding is a strong incentive for preemptive coronary angiography in renal transplant candidates with a smoking history. Ramanathan *et al.* (106) reported that 33% of patients with type 1 and 48% of patients with type 2 diabetes had a significant stenosis ($\geq 70\%$) in at least one coronary artery, and a smoking history increased the risk for CAD by 2%

for each pack-year of smoking. Another important issue is *de novo* congestive heart failure in renal transplant patients. It has a poor prognosis and has been shown to be associated with smoking in 27,011 transplant recipients of the US Renal Data System (107). The available evidence has prompted the National Kidney Foundation Working Groups and European Best Practice Guidelines Expert Group on Renal Transplantations to recommend smoking cessation as an important measure in long-term care of renal transplant recipients.

Smoking Cessation

Benefits of Smoking Cessation in Renal Patients

Only a little information is available concerning the beneficial effects of smoking cessation on the course of renal function. The few studies that investigated this issue all found a positive effect, however. Chase *et al.* (108) observed that in patients who had type 1 diabetes and nephropathy and in whom BP was adequately controlled, cessation of smoking significantly reduced urine albumin excretion, although glycemia was not perfectly controlled. Sawicki *et al.* (109) performed a prospective follow-up study during 1 yr in a sequential sample of 34 smokers, 35 nonsmokers, and 24 ex-smokers with type 1 diabetes, hypertension, and diabetic nephropathy. They reported that progression of diabetic nephropathy was observed in 53% of current smokers but only 33% of ex-smokers (and 11% of nonsmokers). These data were confirmed in patients with type 2 diabetes (110) (progression in 22% of ex-smokers *versus* 42% in smokers [and 23% in nonsmokers]) and by documenting reduction of urine TGF- β_1 excretion as a marker of renal injury after smoking cessation (51). Finally, Sung *et al.* (111) reported that smoking cessation before renal transplantation led to better graft survival as compared with graft recipients who continued smoking after renal transplantation. Taken together, although prospective, randomized intervention studies are lacking, there is sufficient evidence that smoking cessation slows the rate of renal function decline.

Smoking Cessation Strategies in Renal Patients

No studies on the effectiveness of various smoking cessation strategies in renal patients are available. We are aware of one report about the implementation of a clinical practice guideline for treating tobacco use and dependence within a kidney and pancreas transplant program (112). Such a program is of major importance to reduce the astonishingly high rates of posttransplantation smoking after pancreas (113), heart (114), and kidney transplantation (111,115).

Because no randomized, controlled trials on smoking cessation interventions are available in renal patients, we have to rely on data from the general population. Weaning smokers from their habit is a difficult task, and most physicians do not invest sufficient time to address this problem (116,117). Even single minimal interventions are only rarely performed, which is even more true for successive consultations. The concept of stepwise smoking dishabituating is supported by evidence-based consensus recommendations from national and international medical societies and public institutions. Behavioral counseling and extended follow-up are critical to maximize

quit rates (118–120) but may be difficult to adopt because of time constraints and lack of expertise of physicians. It is, however, feasible to perform three easy steps, which should be regarded as mandatory:

First, patients should be asked about their smoking behavior. Those who smoke should be counseled about the adverse health effects, including the less commonly known adverse renal effects of smoking. It cannot be stressed enough that physician advice *per se* is an effective, evidence-based strategy (121). In a second step, those who are motivated to stop smoking should be informed about the possibility of drug support (122), which can double the odds for success (119,123). As first-line treatment, this comprises nicotine replacement therapy (NRT; *via* patch, gum, or nasal spray) alone or in combination with the non-nicotine drug bupropion. There is evidence that combining NRT with bupropion may be more effective than using each drug alone (123). Second-line treatment includes clonidine (122). In our opinion, the use of nortriptyline, varenicline, rimonabant, monoamine oxidase inhibitors, or selective serotonin reuptake inhibitors should be discouraged in renal patients because of insufficient data (even in nonrenal patients) and partially unknown or even peculiar pharmacokinetics in renal failure. The third step should be repeated motivation and advice as an integral part of each further routine consultation.

Concerning pharmacotherapy in patients with impaired renal function, one should be aware that nicotine accumulates in renal failure (124). Reduction of NRT dosage should be envisaged in patients with seriously impaired renal function. A cautious approach is particularly necessary in situations in which the nicotine-related increase in sympathetic activity may have deleterious effects; however, it cannot be expected that NRT is more injurious than continuous smoking. Concerning therapy with bupropion, a dosage reduction in patients with ESRD has been suggested because of significant accumulation of two major active metabolites (125). Before more information is available, a dosage of 150 mg of bupropion, orally, every 3 d in patients who are on renal replacement therapy seems appropriate (125). Concerns that bupropion may increase suicide risk are unproved (126). According to a meta-analysis of 31 trials (126), bupropion doubled the success rate (OR 1.94). Clonidine is also a good choice in renal patients because of its antihypertensive effect, but it is hampered by known adverse effects and has been investigated in only a few trials. According to a meta-analysis of six studies (127), the pooled OR of clonidine *versus* placebo was 1.89.

Conclusions

The dramatic worldwide increase of patients with ESRD urges nephrologists to implement preventive strategies. Smoking emerges as an important modifiable renal risk factor on the basis of (1) multiple studies documenting a clear association of smoking and renal damage in individuals of the general population, patients with diabetes, and hypertensive patients; (2) some studies documenting a beneficial effect of smoking cessation on renal outcome; (3) several studies documenting smoking-related alterations that are proved to be harmful for the

kidney (*e.g.*, an increase in BP); and (4) experimental evidence proving that cigarette smoke affects mediator systems that are known to be players in the genesis of progressive renal damage, both *in vivo* and *in vitro*. Scarcity of data in some areas such as primary renal disease does not implicate absence of evidence. Concerning the adverse effects of smoking on cardiovascular morbidity and mortality in patients with CKD or ESRD, the studies discussed furnish sufficient evidence that smoking confers a similar cardiovascular risk as in the general population.

We hope to have convinced the nephrologic community that motivation of patients to quit smoking should be immediately implemented, because it is certainly the most cost-effective and beneficial strategy against the whole spectrum of CKD, ESRD, and CVD morbidity and mortality in renal patients. The practical guideline for a simple smoking cessation strategy is recommended to be an integral part of renal patient treatment. More sophisticated approaches are needed but are still waiting to be investigated in a clinical study setting.

Disclosures

None.

References

1. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, Atkins RC: Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol* 14: S131–S138, 2003
2. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 41: 1–12, 2003
3. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, Hallan HA, Lydersen S, Holmen J: International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 17: 2275–2284, 2006
4. Kiberd B: The chronic kidney disease epidemic: Stepping back and looking forward. *J Am Soc Nephrol* 17: 2967–2973, 2006
5. White SL, Cass A, Atkins RC, Chadban SJ: Chronic kidney disease in the general population. *Adv Chronic Kidney Dis* 12: 5–13, 2005
6. Dirks JH, de Zeeuw D, Agarwal SK, Atkins RC, Correa-Rotter R, D'Amico G, Bennett PH, El Nahas M, Valdes RH, Kaseje D, Katz IJ, Naicker S, Rodriguez-Iturbe B, Schieppati A, Shaheen F, Sitthi-Amorn C, Solez K, Viberti G, Remuzzi G, Weening JJ, International Society of Nephrology Commission for the Global Advancement of Nephrology Study Group 2004: Prevention of chronic kidney and vascular disease: Toward global health equity—The Bellagio 2004 Declaration. *Kidney Int Suppl* S1–S6, 2005
7. Perico N, Codreanu I, Schieppati A, Remuzzi G: The future of renoprotection. *Kidney Int Suppl* S95–S101, 2005
8. Amann K, Wanner C, Ritz E: Cross-talk between the kidney and the cardiovascular system. *J Am Soc Nephrol* 17: 2112–2119, 2006
9. McCullough PA: Cardiovascular disease in chronic kidney

- disease from a cardiologist's perspective. *Curr Opin Nephrol Hypertens* 13: 591–600, 2004
10. Orth SR: Effects of smoking on systemic and intrarenal hemodynamics: Influence on renal function. *J Am Soc Nephrol* 15[Suppl 1]: S58–S63, 2004
 11. Orth SR: Cigarette smoking: An important risk factor—Far beyond carcinogenesis. *Tob Induced Dis* 1: 137–155, 2002
 12. Orth SR: Smoking and the kidney. *J Am Soc Nephrol* 13: 1663–1672, 2002
 13. ANZDATA Registry: Annual report. Available at: <http://www.anzdata.org.au/anzdata/AnzdataReport/29thReport/Ch02NewPatients.pdf>. Accessed November 6, 2007
 14. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J: Blood pressure and end-stage renal disease in men. *N Engl J Med* 334: 13–18, 1996
 15. Pinto-Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de Zeeuw D, de Jong PE: Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med* 133: 585–591, 2000
 16. Halimi JM, Giraudeau B, Vol S, Cacès E, Nivet H, Lebranchu Y, Tichet J: Effects of current smoking and smoking discontinuation on renal function and proteinuria in the general population. *Kidney Int* 58: 1285–1292, 2000
 17. Briganti EM, Branley P, Chadban SJ, Shaw JE, McNeil JJ, Welborn TA, Atkins RC: Smoking is associated with renal impairment and proteinuria in the normal population: The AusDiab kidney study. Australian Diabetes, Obesity and Lifestyle Study. *Am J Kidney Dis* 40: 704–712, 2002
 18. Orth SR, Ritz E: Adverse effect of smoking on renal function in the general population: Are men at higher risk? *Am J Kidney Dis* 40: 864–866, 2002
 19. Bleyer AJ, Shemanski LR, Burke GL, Hansen KJ, Appel RG: Tobacco, hypertension, and vascular disease: Risk factors for renal functional decline in an older population. *Kidney Int* 57: 2072–2079, 2000
 20. Verhave JC, Hillege HL, Burgerhof JG, Gansevoort RT, de Zeeuw D, de Jong PE, PREVEND Study Group: The association between atherosclerotic risk factors and renal function in the general population. *Kidney Int* 67: 1967–1973, 2005
 21. Vupputuri S, Sandler DP: Lifestyle risk factors and chronic kidney disease. *Ann Epidemiol* 13: 712–720, 2003
 22. Haroun MK, Jaar BG, Hoffman SC, Comstock GW, Klag MJ, Coresh J: Risk factors for chronic kidney disease: A prospective study of 23,534 men and women in Washington County, Maryland. *J Am Soc Nephrol* 14: 2934–2941, 2003
 23. Ishani A, Grandits GA, Grimm RH, Svendsen KH, Collins AJ, Prineas RJ, Neaton JD: Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. *J Am Soc Nephrol* 17: 1444–1452, 2006
 24. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shigai T, Narita M, Koyama A: Risk factors for chronic kidney disease in a community-based population: A 10-year follow-up study. *Kidney Int* 71: 159–166, 2007
 25. Hallan S, de Mutsert R, Carlsen S, Dekker FW, Aasarød K, Holmen J: Obesity, smoking, and physical inactivity as risk factors for CKD: Are men more vulnerable? *Am J Kidney Dis* 47: 396–405, 2006
 26. Baggio B, Budakovic A, Perissinotto E, Maggi S, Cantaro S, Enzi G, Grigoletto F, ILSA Working Group: Atherosclerotic risk factors and renal function in the elderly: The role of hyperfibrinogenemia and smoking. Results from the Italian Longitudinal Study on Ageing (ILSA). *Nephrol Dial Transplant* 20: 114–123, 2005
 27. Joshi VD, Mooppil N, Lim J: Prevalence and risk factors of undetected proteinuria in an elderly South-East Asian population. *Nephrology (Carlton)* 11: 347–354, 2006
 28. Ejerblad E, Fored CM, Lindblad P, Fryzek J, Dickman PW, Elinder CG, McLaughlin JK, Nyren O: Association between smoking and chronic renal failure in a nationwide population-based case-control study. *J Am Soc Nephrol* 15: 2178–2185, 2004
 29. de Boer IH, Sibley SD, Kestenbaum B, Sampson JN, Young B, Cleary PA, Steffes MW, Weiss NS, Brunzell JD, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group: Central obesity, incident microalbuminuria, and change in creatinine clearance in the epidemiology of diabetes interventions and complications study. *J Am Soc Nephrol* 18: 235–243, 2007
 30. Rossing K, Christensen PK, Hovind P, Tarnow L, Rossing P, Parving HH: Progression of nephropathy in type 2 diabetic patients. *Kidney Int* 66: 1596–1605, 2004
 31. Chuahirun T, Wesson DE: Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. *Am J Kidney Dis* 39: 376–382, 2002
 32. Keeton GR, Smit RZ, Bryer A: Renal outcome of type 2 diabetes in South Africa: A 12-year follow-up study. *S Afr Med J* 94: 771–775, 2004
 33. Scott LJ, Warram JH, Hanna LS, Laffel LM, Ryan L, Krolewski AS: A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. *Diabetes* 50: 2842–2849, 2001
 34. Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG: Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: A global perspective. *Kidney Int* 69: 2057–2063, 2006
 35. Orth SR, Schroeder T, Ritz E, Ferrari P: Effects of smoking on renal function in patients with type 1 and type 2 diabetes mellitus. *Nephrol Dial Transplant* 20: 2414–2419, 2005
 36. Warmoth L, Regalado MM, Simoni J, Harrist RB, Wesson DE: Cigarette smoking enhances increased urine albumin excretion as a risk factor for glomerular filtration rate decline in primary hypertension. *Am J Med Sci* 330: 111–119, 2005
 37. Perry HM Jr, Miller JP, Fornoff JR, Baty JD, Sambhi MP, Rutan G, Moskowitz DW, Carmody SE: Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 25: 587–594, 1995
 38. Orth SR, Stockmann A, Conradt C, Ritz E, Ferro M, Kreuzer W, Piccoli G, Rambašek M, Roccatello D, Schäfer K, Sieberth HG, Wanner C, Watschinger B, Zucchelli P: Smoking as a risk factor for end-stage renal failure in men with primary renal disease. *Kidney Int* 54: 926–931, 1998
 39. Paterson AD, Magistroni R, He N, Wang K, Johnson A, Fain PR, Dicks E, Parfrey P, St George-Hyslop P, Pei Y: Progressive loss of renal function is an age-dependent heritable trait in type 1 autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 16: 755–762, 2005

40. Font J, Ramos-Casals M, Cervera R, García-Carrasco M, Torras A, Sisó A, Darnell A, Ingelmo M: Cardiovascular risk factors and the long-term outcome of lupus nephritis. *QJM* 94: 19–26, 2001
41. Ward MM, Studenski S: Clinical prognostic factors in lupus nephritis: The importance of hypertension and smoking. *Arch Intern Med* 152: 2082–2088, 1992
42. Joosten SA, Sijpkens YW, van Kooten C, Paul LC: Chronic renal allograft rejection: pathophysiologic considerations. *Kidney Int* 68: 1–13, 2005
43. Lin SJ, Koford JK, Baird BC, Hurdle JF, Krikov S, Habib AN, Goldfarb-Rumyantsev AS: Effect of donors' intravenous drug use, cigarette smoking, and alcohol dependence on kidney transplant outcome. *Transplantation* 80: 482–486, 2005
44. Matas AJ, Payne WD, Sutherland DE, Humar A, Gruessner RW, Kandaswamy R, Dunn DL, Gillingham KJ, Najarian JS: 2,500 living donor kidney transplants: A single-center experience. *Ann Surg* 234: 149–164, 2001
45. Zitt N, Kollerits B, Neyer U, Mark W, Heining D, Mayer G, Kronenberg F, Lhotka K: Cigarette smoking and chronic allograft nephropathy. *Nephrol Dial Transplant* 22: 3034–3039, 2007
46. Fellstrom B, Holdaas H, Jardine AG, Nyberg G, Gronhagen-Riska C, Madsen S, Neumayer HH, Cole E, Maes B, Ambuhl P, Olsson AG, Staffler B, Pedersen TR, Assessment of Lescol in Renal Transplantation Study Investigators: Risk factors for reaching renal endpoints in the assessment of Lescol in renal transplantation (ALERT) trial. *Transplantation* 79: 205–212, 2005
47. Odoni G, Ogata H, Viedt C, Amann K, Ritz E, Orth SR: Cigarette smoke condensate aggravates renal injury in the renal ablation model. *Kidney Int* 61: 2090–2098, 2002
48. Jaimes EA, Tian RX, Raij L: Nicotine: The link between cigarette smoking and the progression of renal injury? *Am J Physiol Heart Circ Physiol* 292: H76–H82, 2007
49. Dasgupta P, Chellappan SP: Nicotine-mediated cell proliferation and angiogenesis: New twists to an old story. *Cell Cycle* 5: 2324–2328, 2006
50. Mur C, Claria J, Rodela S, Lario S, Campistol JM, Titos E, Iñigo P, Cases A, Abián J, Esmatjes E: Cigarette smoke concentrate increases 8-epi-PGF₂α and TGFβ₁ secretion in rat mesangial cells. *Life Sci* 75: 611–621, 2004
51. Chuahirun T, Simoni J, Hudson C, Seipel T, Khanna A, Harrist RB, Wesson DE: Cigarette smoking exacerbates and its cessation ameliorates renal injury in type 2 diabetes. *Am J Med Sci* 327: 57–67, 2004
52. Esmatjes E, Flores L, Lario S, Claria J, Cases A, Iñigo P, Campistol JM: Smoking increases serum levels of transforming growth factor-beta in diabetic patients. *Diabetes Care* 22: 1915–1916, 1999
53. Cucina A, Corvino V, Sapienza P, Borrelli V, Lucarelli M, Scarpa S, Strom R, Santoro-D'Angelo L, Cavallaro A: Nicotine regulates basic fibroblastic growth factor and transforming growth factor beta₁ production in endothelial cells. *Biochem Biophys Res Commun* 257: 306–312, 1999
54. Galazyn-Sidorczuk M, Brzoska MM, Moniuszko-Jakoniuk J: Estimation of Polish cigarettes contamination with cadmium and lead, and exposure to these metals via smoking. *Environ Monit Assess* May 17, 2007 [pub ahead of print]
55. Barbier O, Jacquillet G, Tauc M, Cougnon M, Poujeol P: Effect of heavy metals on, and handling by, the kidney. *Nephron Physiol* 99: 105–110, 2005
56. EL Safty IA, Afifi AM, Shouman AE, EL Sady AK: Effects of smoking and lead exposure on proximal tubular integrity among Egyptian industrial workers. *Arch Med Res* 35: 59–65, 2004
57. EL Safty IA, Shouman AE, Amin NE: Nephrotoxic effects of mercury exposure and smoking among Egyptian workers in a fluorescent lamp factory. *Arch Med Res* 34: 50–55, 2003
58. EL Safty IA, Gadallah M, Shouman AE, Nessim DE: Subclinical nephrotoxicity caused by smoking and occupational silica exposure among Egyptian industrial workers. *Arch Med Res* 34: 415–421, 2003
59. Satarug S, Ujjin P, Vanavanitkun Y, Nishijo M, Baker JR, Moore MR: Effects of cigarette smoking and exposure to cadmium and lead on phenotypic variability of hepatic CYP2A6 and renal function biomarkers in men. *Toxicology* 204: 161–173, 2004
60. Diamond GL, Thayer WC, Choudhury H: Pharmacokinetics/pharmacodynamics (PK/PD) modeling of risks of kidney toxicity from exposure to cadmium: Estimates of dietary risks in the U.S. population. *J Toxicol Environ Health A* 66: 2141–2164, 2003
61. Ikeda M, Ezaki T, Moriguchi J, Fukui Y, Okamoto S, Ukai H, Sakurai H: No meaningful increase in urinary tubular dysfunction markers in a population with 3 microg cadmium/g creatinine in urine. *Biol Trace Elem Res* 113: 35–44, 2006
62. Satarug S, Moore MR: Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. *Environ Health Perspect* 112: 1099–1103, 2004
63. Omvik P: How smoking affects blood pressure. *Blood Press* 5: 71–77, 1996
64. Hansen KW, Pedersen MM, Christiansen JS, Mogensen CE: Night blood pressure and cigarette smoking: Disparate association in healthy subjects and diabetic patients. *Blood Press* 3: 381–388, 1994
65. Davidson MB, Hix JK, Vidt DG, Brotman DJ: Association of impaired diurnal blood pressure variation with a subsequent decline in glomerular filtration rate. *Arch Intern Med* 166: 846–852, 2006
66. Giles TD: Circadian rhythm of blood pressure and the relation to cardiovascular events. *J Hypertens Suppl* 24: S11–S16, 2006
67. Trap-Jensen J: Effects of smoking on the heart and peripheral circulation. *Am Heart J* 115: 263–267, 1988
68. Matsui Y, Kario K, Ishikawa J, Hoshida S, Eguchi K, Shimada K: Smoking and antihypertensive medication: Interaction between blood pressure reduction and arterial stiffness. *Hypertens Res* 28: 631–638, 2005
69. Benck U, Clorius JH, Zuna I, Ritz E: Renal hemodynamic changes during smoking: Effects of adrenoceptor blockade. *Eur J Clin Invest* 29: 1010–1018, 1999
70. Bangstad HJ, Osterby R, Rudberg S, Hartmann A, Brabrand K, Hanssen KF: Kidney function and glomerulopathy over 8 years in young patients with type I (insulin-dependent) diabetes mellitus and microalbuminuria. *Diabetologia* 45: 253–261, 2002
71. Baggio B, Budakovic A, Dalla Vestra M, Saller A, Bruseghin M, Fioretto P: Effects of cigarette smoking on glomer-

- ular structure and function in type 2 diabetic patients. *J Am Soc Nephrol* 13: 2730–2736, 2002
72. Lhotta K, Rumpelt HJ, Konig P, Mayer G, Kronenberg F: Cigarette smoking and vascular pathology in renal biopsies. *Kidney Int* 61: 648–654, 2002
 73. Myllymaki J, Honkanen T, Syrjanen J, Helin H, Rantala I, Pasternack A, Mustonen J: Uric acid correlates with the severity of histopathological parameters in IgA nephropathy. *Nephrol Dial Transplant* 20: 89–95, 2005
 74. Goforth RL, Rennke H, Sethi S: Renal vascular sclerosis is associated with inherited thrombophilias. *Kidney Int* 70: 743–750, 2006
 75. Markowitz GS, Lin J, Valeri AM, Avila C, Nasr SH, D'Agati VD: Idiopathic nodular glomerulosclerosis is a distinct clinicopathologic entity linked to hypertension and smoking. *Hum Pathol* 33: 826–835, 2002
 76. Kuppachi S, Idris N, Chander PN, Yoo J: Idiopathic nodular glomerulosclerosis in a non-diabetic hypertensive smoker: Case report and review of literature. *Nephrol Dial Transplant* 21: 3571–3575, 2006
 77. Nasr SH, D'Agati VD: Nodular glomerulosclerosis in the nondiabetic smoker. *J Am Soc Nephrol* 18: 2032–2036, 2007
 78. Liang KV, Greene EL, Oei LS, Lewin M, Lager D, Sethi S: Nodular glomerulosclerosis: Renal lesions in chronic smokers mimic chronic thrombotic microangiopathy and hypertensive lesions. *Am J Kidney Dis* 49: 552–559, 2007
 79. United States Renal Data System: *USRDS Annual Data Report*. Available at http://www.usrds.org/adr_2006.htm. Accessed November 6, 2007
 80. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX: Chronic kidney disease and mortality risk: A systematic review. *J Am Soc Nephrol* 17: 2034–2047, 2006
 81. Muntner P, He J, Hamm L, Loria C, Whelton PK: Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 13: 745–753, 2002
 82. Jungers P, Massy ZA, Nguyen Khoa T, Fumeron C, Labrunie M, Lacour B, Descamps-Latscha B, Man NK: Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: A prospective study. *Nephrol Dial Transplant* 12: 2597–2602, 1997
 83. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, Psaty B: Cardiovascular mortality risk in chronic kidney disease: Comparison of traditional and novel risk factors. *JAMA* 293: 1737–1745, 2005
 84. Muntner P, He J, Astor BC, Folsom AR, Coresh J: Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: Results from the Atherosclerosis Risk in Communities study. *J Am Soc Nephrol* 16: 529–538, 2005
 85. de Vinuesa SG, Ortega M, Martinez P, Goicoechea M, Campdera FG, Luño J: Subclinical peripheral arterial disease in patients with chronic kidney disease: Prevalence and related risk factors. *Kidney Int Suppl* S44–S47, 2005
 86. Stack AG: Coronary artery disease and peripheral vascular disease in chronic kidney disease: An epidemiological perspective. *Cardiol Clin* 23: 285–298, 2005
 87. Selvin E, Erlinger TP: Prevalence of and risk factors for peripheral arterial disease in the United States: Results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 110: 738–743, 2004
 88. Myllymaki J, Syrjanen J, Helin H, Pasternack A, Kattainen A, Mustonen J: Vascular diseases and their risk factors in IgA nephropathy. *Nephrol Dial Transplant* 21: 1876–1882, 2006
 89. Chan WB, Chan NN, Lai CW, So WY, Lo MK, Lee KF, Chow CC, Metreweli C, Chan JC: Vascular defect beyond the endothelium in type II diabetic patients with overt nephropathy and moderate renal insufficiency. *Kidney Int* 70: 711–716, 2006
 90. Cao JJ, Arnold AM, Manolio TA, Polak JF, Psaty BM, Hirsch CH, Kuller LH, Cushman M: Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: The Cardiovascular Health Study. *Circulation* 116: 32–38, 2007
 91. London GM, Marchais SJ, Guerin AP, Metivier F: Arteriosclerosis, vascular calcifications and cardiovascular disease in uremia. *Curr Opin Nephrol Hypertens* 14: 525–531, 2005
 92. Koch M, Trapp R, Kulas W, Grabensee B: Critical limb ischaemia as a main cause of death in patients with end-stage renal disease: A single-centre study. *Nephrol Dial Transplant* 19: 2547–2552, 2004
 93. Rajagopalan S, Dellegrottaglie S, Furniss AL, Gillespie BW, Satayathum S, Lameire N, Saito A, Akiba T, Jadoul M, Ginsberg N, Keen M, Port FK, Mukherjee D, Saran R: Peripheral arterial disease in patients with end-stage renal disease: Observations from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Circulation* 114: 1914–1922, 2006
 94. Stack AG, Bloembergen WE: Prevalence and clinical correlates of coronary artery disease among new dialysis patients in the United States: A cross-sectional study. *J Am Soc Nephrol* 12: 1516–1523, 2001
 95. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, Teehan BP, Levey AS: Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. *Kidney Int* 58: 353–362, 2000
 96. Di Benedetto A, Marcelli D, D'Andrea A, Cice G, D'Isa S, Cappabianca F, Pacchiano G, D'Amato R, Oggero AR, Bonanno D, Pergamo O, Calabrò R: Risk factors and underlying cardiovascular diseases in incident ESRD patients. *J Nephrol* 18: 592–598, 2005
 97. Foley RN, Herzog CA, Collins AJ: Smoking and cardiovascular outcomes in dialysis patients: The United States Renal Data System Wave 2 study. *Kidney Int* 63: 1462–1467, 2003
 98. Zoccali C, Tripepi G, Mallamaci F: Predictors of cardiovascular death in ESRD. *Semin Nephrol* 25: 358–362, 2005
 99. Ojo AO: Cardiovascular complications after renal transplantation and their prevention. *Transplantation* 82: 603–611, 2006
 100. Kasiske BL, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ: Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 7: 158–165, 1996
 101. Cardinal H, Hebert MJ, Rahme E, Houde I, Baran D, Masse M, Boucher A, Le Lorier J, Elderly Recipients Transplant Group: Modifiable factors predicting patient survival in elderly kidney transplant recipients. *Kidney Int* 68: 345–351, 2005
 102. Cosio FG, Falkenhain ME, Pesavento TE, Yim S, Alamir A,

- Henry ML, Ferguson RM: Patient survival after renal transplantation: II. The impact of smoking. *Clin Transplant* 13: 336–341, 1999
103. Ponticelli C, Villa M, Cesana B, Montagnino G, Tarantino A: Risk factors for late kidney allograft failure. *Kidney Int* 62: 1848–1854, 2002
104. Yango AF, Gohh RY, Monaco AP, Reinert SE, Gautam A, Dworkin LD, Morrissey PE: Excess risk of renal allograft loss and early mortality among elderly recipients is associated with poor exercise capacity. *Clin Nephrol* 65: 401–407, 2006
105. Chuang P, Gibney EM, Chan L, Ho PM, Parikh CR: Predictors of cardiovascular events and associated mortality within two years of kidney transplantation. *Transplant Proc* 36: 1387–1391, 2004
106. Ramanathan V, Goral S, Tanriover B, Feurer ID, Kazancioğlu R, Shaffer D, Helderman JH: Screening asymptomatic diabetic patients for coronary artery disease prior to renal transplantation. *Transplantation* 79: 1453–1458, 2005
107. Lentine KL, Schnitzler MA, Abbott KC, Li L, Burroughs TE, Irish W, Brennan DC: De novo congestive heart failure after kidney transplantation: A common condition with poor prognostic implications. *Am J Kidney Dis* 46: 720–733, 2005
108. Chase HP, Garg SK, Marshall G, Berg CL, Harris S, Jackson WE, Hamman RE: Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA* 265: 614–617, 1991
109. Sawicki PT, Didjurgeit U, Muhlhauser I, Bender R, Heineemann L, Berger M: Smoking is associated with progression of diabetic nephropathy. *Diabetes Care* 17: 126–131, 1994
110. Gambaro G, Bax G, Fusaro M, Normanno M, Manani SM, Zanella M, Dangelo A, Fedele D, Favaro S: Cigarette smoking is a risk factor for nephropathy and its progression in type 2 diabetes mellitus. *Diabetes Nutr Metab* 14: 337–342, 2001
111. Sung RS, Althoen M, Howell TA, Ojo AO, Merion RM: Excess risk of renal allograft loss associated with cigarette smoking. *Transplantation* 71: 1752–1757, 2001
112. Ehlers SL, Rodrigue JR, Patton PR, Lloyd-Turner J, Kaplan B, Howard RJ: Treating tobacco use and dependence in kidney transplant recipients: Development and implementation of a program. *Prog Transplant* 16: 33–37, 2006
113. Larsen JL, Colling CW, Ratanasuwana T, Burkman TW, Lynch TG, Erickson JM, Lyden ER, Lane JT, Mack-Shipman LR: Pancreas transplantation improves vascular disease in patients with type 1 diabetes. *Diabetes Care* 27: 1706–1711, 2004
114. Nagele H, Kalmar P, Rodiger W, Stubbe HM: Smoking after heart transplantation: An underestimated hazard? *Eur J Cardiothorac Surg* 12: 70–74, 1997
115. Kheradmand A, Shahbazian H: The role of pretransplant smoking on allograft survival in kidney recipients. *Urol J* 2: 36–39, 2005
116. NIH State-of-the-Science Conference statement on tobacco use: Prevention, cessation, and control: *NIH Consens State Sci Statements* 23: 1–26, 2006
117. Martinez-Ramirez HR, Jalomo-Martinez B, Cortés-Sanabria L, Rojas-Campos E, Barragán G, Alfaro G, Cueto-Manzano AM: Renal function preservation in type 2 diabetes mellitus patients with early nephropathy: A comparative prospective cohort study between primary health care doctors and a nephrologist. *Am J Kidney Dis* 47: 78–87, 2006
118. Feinson JA, Chidekel AS: What physicians can do about the tobacco problem: Best practice interventions for your practice and office. *Del Med J* 78: 137–145, 2006
119. Nides M, Leischow S, Sarna L, Evans SE: Maximizing smoking cessation in clinical practice: Pharmacologic and behavioral interventions. *Prev Cardiol* 10: 23–30, 2007
120. Pederson LL, Blumenthal D: Smoking cessation: What works in primary care settings. *Ethn Dis* 15: S10–S13, 2005
121. Hobbs SD, Bradbury AW: Smoking cessation strategies in patients with peripheral arterial disease: An evidence-based approach. *Eur J Vasc Endovasc Surg* 26: 341–347, 2003
122. Frishman WH: Smoking cessation pharmacotherapy: Nicotine and non-nicotine preparations. *Prev Cardiol* 10: 10–22, 2007
123. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramoto ML, Daughton DM, Doan K, Fiore MC, Baker TB: A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 340: 685–691, 1999
124. Molander L, Hansson A, Lunell E, Alaintalo L, Hoffmann M, Larsson R: Pharmacokinetics of nicotine in kidney failure. *Clin Pharmacol Ther* 68: 250–260, 2000
125. Worrall SP, Almond MK, Dhillon S: Pharmacokinetics of bupropion and its metabolites in haemodialysis patients who smoke: A single dose study. *Nephron Clin Pract* 97: c83–c89, 2004
126. Hughes JR, Stead LF, Lancaster T: Antidepressants for smoking cessation. *Cochrane Database Syst Rev* CD000031, 2007
127. Gourlay SG, Stead LF, Benowitz NL: Clonidine for smoking cessation. *Cochrane Database Syst Rev* CD000058, 2004